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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MACFARLANE, STACEY NEE	

ART UNIT	PAPER NUMBER
1649	

NOTIFICATION DATE	DELIVERY MODE
10/12/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatentMail@ropesgray.com
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Office Action Summary	Application No.	Applicant(s)	
	09/739,933	REID ET AL.	
	Examiner	Art Unit	
	STACEY MACFARLANE	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,2,6-8,65,66,70-72 and 74* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,2,6-8,65,66,70-72 and 74* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/12/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 12, 2011 has been entered.

Response to Amendment

2. Claims 5, 33 and 63-64 have been cancelled, Claims 1 and 70-72 have been amended and Claim 74 newly added as requested in the amendment filed on August 12, 2011. Following the amendment, claims 1, 2, 6-8, 65, 66, 70-72 and 74 are pending in the instant application and are under examination in the instant office action.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. As currently amended, Claims 1, 2, 6-8, 65, 66, 70-72 and 74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. As currently amended, Claims 1 and 70 are vague and indefinite. The claims have been amended to specifically exclude the striatum, however, the claims still recite

the internal capsule and encompass areas adjacent to the subependymal zone. It is well-recognized within the art that the internal capsule is a white matter tract within the corpus striatum that separates the caudate nucleus from the putamen/globus pallidus. This white matter tract gives the striatum the striped or "striated" appearance from which its name is derived. Additionally, it is recognized that the subependymal zone (SEZ) is the floor of the lateral ventricles and the immediate adjacent tissue is the parenchyma of the striatum. Even within the current state of the art it is unclear where the boundaries of the end and the striatum begin (sentence bridging columns, page 2913 of Kazanis, Brain, 132(11):2909-2921, 2009).

8. Claim 2 is missing active method steps by which differentiation of the neural progenitor cell or their progeny is achieved. Absent such steps the claim appears to merely encompass a result of the administration step then it fails to further limit.

9. On page 9 of Remarks filed August 12, 2011, Applicant traverses the rejection on the grounds that the active step is set forth in claim 1, administration of TGF-alpha and that the claim is a result of that active step, reciting that administration also effects differentiation of the cells, and that assays to detect differentiated neurons are disclosed in the specification.

10. This is not found persuasive because Applicant is essentially stating that the claim does not further limit the method but recites an effect of administration. Furthermore, the active steps for assessing differentiation of the progenitor cells or progeny in vivo are not claimed. The rejection is maintained.

11. Claim 8 is indefinite in that it recites essentially treatment of damage at "spinal nerve root origins" which a skilled artisan would recognize as the dorsal or ventral roots of the spinal cord but the claim fails to relate how administration at sites within the pallidum, septum, cortex, external or internal capsule, substantia nigra-ventral tegmentum or ependymal or subependymal zones and their adjacent structures mediate effects in the spinal nerve roots.

12. Applicant traverse the rejection on pages 9-10 of Remarks (*Id*) on the ground that the tissue having damage encompasses any tissue within the CNS and spinal cord and these differ from the sites of administration.

13. This is not found persuasive because the claim is still missing an essential step that connects administration within the brain to treatment within the spinal cord. The rejection is maintained.

14. Claim 65 is indefinite in that it recites administration for a period of “at least about sixteen days”. The court has held that claims reciting "at least about" were indefinite where there was close prior art and there was nothing in the specification, prosecution history, or the prior art to provide any indication as to what range of specific activity is covered by the term "about." Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991). Within the specification there is only an exemplary guidance: “typically perfused one to 16 days postlesion (3-18 days of infusion)” (paragraph [0223]). Therefore, the metes and bounds of “about” within the claim are unclear.

15. Claim 66 is indefinite in that the claim recites administration is "initiated weeks after the occurrence of the damage or lesion". The claim appears to be missing essential method steps whereby damage is diagnosed and the period of time following damage has been determined.

16. Claim 72 is indefinite in that it claims the method of claims 66 or 70 wherein the progenitor cell or progeny thereof is from the ependymal zone. There is no method steps recited whereby the lineage of the progenitor cell and/or its progeny is determined in vivo.

17. Claims 6, 7, 71 and 74 are indefinite for depending from indefinite claims.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

As currently amended, Claims 65 and 74 are rejected under 35 U.S.C. 102(b) as being anticipated by Loughlin et al. (1992) for reasons of record in the previous action.

On pages 11-13 of Remarks (Id), Applicant traverses the rejection on the grounds that the Loughlin Abstract is directed to testing a hypothesis that TGF-alpha might play a role in the efficacy of transplants and concludes that its role is purely speculative. Applicant sites another Loughlin (1994) book chapter that states similar findings, and argues that there is no teaching of attracting neural progenitor cell or

progeny to a site of CNS damage. Applicant argues that Loughlin does not teach administration for about sixteen days and therefore claim 65 distinguishes from the reference.

While this has been considered in full it is not persuasive because the Loughlin art teaches TGF-alpha intrastriatal infusion into the brain "over a two week period" and report amelioration of behavioral deficits. As stated above, the metes and bounds of "about sixteen days" is unclear in view of what little guidance there is for this recitation within the specification. The disclosure only provides exemplary guidance of infusions for "3-18 days" (paragraph [0223]). Thus, the two week period taught by the Loughlin prior art falls within the range of "about" sixteen as taught by the specification.

Furthermore, even though the mechanism of action, namely, attracting neural progenitor cells and their progeny to a site of injury, is not explicitly set forth in Loughlin, the sole active step of administration is anticipated and the resultant step indicating the success of the method (amelioration of behavioral deficit) is explicitly achieved. Therefore, the Examiner maintains that the claimed effect of administration (attracting neural progenitor cells and their progeny to a site of injury) does not render something which is old as patentable. Applicant has not set forth evidence that the Loughlin et al. prior art does not necessarily or inherently possess the characteristics of Applicant's claimed product. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. As currently amended, Claims 1, 2, 6-8, 65, 66, 70-72 and 74 stand as rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Loughlin et al. (1992) and Weiss et al. US Patent 5,980,885, filed June 7, 1995, for reasons of record in the previous Office action.

On pages 13-17 of Remarks, Applicant traverses the rejection on the following grounds. Applicant argues that the amendments to the claims render the invention not obvious over the art because Loughlin fails to teach administration outside of the striatum (now excluded from the claims) and there is no suggestion of benefits when administered outside the striatum. Applicant further argues the art fails to teach the requirement of the claim that "the administration effects migration of neural progenitor cells or their progeny to a site of damage of lesion in the CNS as evidenced by an amelioration of behavioral effects" (page 15). Applicant further argues that the hypothesis and mechanism of Loughlin is different than the claims and the reference fails to teach administration for about sixteen days and therefore claim 65 distinguishes from the reference.

While these arguments have been reviewed in full they are not found persuasive for the following reasons. As stated above, Claims 65 and 66 are taught by the

Loughlin prior art which discloses TGF-alpha intrastriatal infusion into the brain "over a two week period" which falls within the "about sixteen days" in view of the "3-18 days" range disclosed in the instant specification. And Loughlin explicitly discloses behavioral deficit amelioration.

While Loughlin only teaches intrastriatal infusion, now excluded from instant claims 1 and 70, the Weiss et al. prior art remedies this deficit by teaching administration of growth factors, including TGF-alpha, to areas outside the striatum, namely, the basal gangia, caudate, putamen, nucleus basalis or substantia nigra (column 23, lines 4-21). Importantly, while both prior art references teach the sole active step of the method (administration of TGF-alpha within the brain), the Weiss Patent teaches the identical mechanism as disclosed in the instant application: growth factor administration to the brain in vivo leads to the generation of large numbers of undifferentiated neural cells arising from the ependymal zone (Column 13, lines 21-41) for the treatment of neurodegenerative disease or trauma (Column 11, lines 40-66) at sites apart from the injection site, including "cerebral cortex, cerebellum, midbrain, brainstem, spinal cord and ventricular tissue, and areas of the PNS including the carotid body and the adrenal medulla. Preferred areas include regions in the basal ganglia, preferably the striatum which consists of the caudate and putamen, or various cell groups such as the globus pallidus, the subthalamic nucleus, the nucleus basalis which is found to be degenerated in Alzheimer's Disease patients, or the substantia nigra pars compacta which is found to be degenerated in Parkinson's Disease patients" (paragraph bridging Columns 12 and 13). Additionally, one of the examples within the Weiss

Patent discloses the Weaver animal model for Parkinson's that have approximately 70% of the dopaminergic neurons of the substantia nigra lost by the age of 3 months. The Weiss Patent experiment teaches utilizing animals that are 3.5 months old (Column 60, lines 58-67), thereby teaching the deficit of the Loughlin reference regarding "administration … initiated weeks after … damage or lesion", required by Claim 66.

Therefore, the Examiner maintains that the invention as a whole is unpatentable over the combination of the Loughlin and Weiss prior art, and the Claims are rejected.

Double Patenting

21. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

22. Claims 1, 5, 6, 33, 63, 65 and 70-72 stand as provisionally rejected on the grounds of provisional nonstatutory obviousness-type double patenting as being unpatentable over claims 45, 48, 55 and 57-60 of copending Application No. 09/129,028.

23. Applicant has not traversed this rejection but has requested that it be held in abeyance until allowable subject matter is identified.

24. Claims 1, 5, 6, 33, 63, 65 and 70-72 are provisionally rejected on the ground of provisional nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 12-13, 41, 43, 53, 54 and 61-65 of copending Application No. 10/167,384.

25. Applicant has not traversed this rejection but has requested that it be held in abeyance until allowable subject matter is identified.

26. Applicants are advised that traversal of the above rejections at a later date, presuming the claims stand substantively as they are now, will not be considered to be timely.

Conclusion

27. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is (571)270-3057. The examiner can normally be reached on M-R 5:45 to 3:30, TELEWORK-Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stacey MacFarlane
Examiner
Art Unit 1649

/Lorraine Spector/
Primary Examiner, Art Unit 1647